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The Sense of Taste: Neurobiology, Aging, and Medication Effects

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ABSTRACT: The sense of taste is an oral chemical sense in mammals that is involved in the choice of foods. Initial transduction of taste stimuli occurs in taste buds, which are distributed in four discrete fields in the oral cavity. Medications can affect the taste buds and ion channels in taste-bud cell membranes involved in stimulus transduction. The sense of taste gradually declines with aging, with bitter taste most affected. Neural circuits that mediate taste in primates include cranial nerves VII, IX, and X, the solitary nucleus in the brain stem, the ventroposteromedial nucleus of the thalamus, and the insular-opercular cortex. The central taste pathways process taste information about sweet, salty, sour, and bitter stimuli serially and in parallel. Medications associated with "metallic" dysgeusia and taste losses affect the taste system via unknown mechanisms.

KEY WORDS: taste, medications, aging.

I. INTRODUCTION

This article is primarily a review of the basic neurobiology of the sense of taste. Critical issues are addressed by citing selected recent studies, except when classic or unique studies are all that are available. Recent reviews that cover most topics more thoroughly are also cited. The assumption is that clinical phenomena cannot be understood until the structure and function of the taste system are defined. Effects of aging and medications on taste are described within the context of the relevant biology. Drug effects and aging effects on the perception of a specific taste quality are discussed in the context of signal transduction of that stimulus quality. Effects of cytotoxic drugs on taste perception and effects of aging on taste-bud numbers are discussed within the context of the biology of taste buds. Drugs that may affect appetite via the taste central nervous system and drugs that serve as unconditioned stimuli for learned flavor aversions are discussed in the context of appetite and flavor aversions. Finally, medications that result in taste losses and metallic dysgeusia are discussed in the context of taste disorders.

The sense of taste is an oropharyngeal chemical sense that is activated during eating, drinking, and food sampling in humans. The taste system evaluates potential food for beneficial (nutritional) and deleterious (poisonous) chemical features. The taste system contributes to the control of salivation and swallowing, reflexes of ingestion and egestion and motivational systems required for eating, and it mediates conscious taste sensations. With aging, ratings of stimulus intensity are reduced in the chemical senses of taste and smell (Cowart, 1989), which are often

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co-activated. However, taste thresholds may not increase as much as smell thresholds with aging (Cowart, 1989). To the degree aging affects taste sensations, loss of interest in nutritious food may develop in the elderly. Taste supplements may be added to foods to increase intake (Schiffman and Warwick, 1989). Attractive tastes are used in designing food, beverage, and oral health-care products to increase markets and compliance, sometimes without consumer health in mind. Useful medications often have unattractive bitter tastes that require masking. Foods and medications can be sweetened or salted to potentially harmful levels. Overindulgence of the sweet or salty tastes contributes to serious common health problems, including obesity, hypertension, and destruction of hard and soft tissues in the oral cavity. The attractiveness of these tastes may be innate but can be nurtured or controlled by experience (Schulkin, 1991). Yet, the elderly, whose sense of taste is reduced, prefer stronger concentrations of sweet and salty stimuli than do younger people (Murphy and Withee, 1986). Local or systemic medications can reduce or distort the sense of taste (Rollin, 1978; Schiffman, 1983; Mott, 1991). Considering the elementary value of the sense of taste to human health and the modern emphasis on preventive medicine, taste physiology and anatomy have been studied sparsely.

II. THE CHEMICAL DIMENSIONS OF TASTE

An accurate definition of the sense of taste in humans is not derived as easily as it may seem. People describe chemical sensory experiences as tastes if they are associated with food, even when other chemosensory systems are involved. As a consequence of this confusion, patients frequently present with "taste" problems who have demonstrably normal taste systems but olfactory deficits (Gent *et al.*, 1987). Using chemical stimuli that neither smell nor irritate, psychophysicists have divided "pure" taste stimuli into four qualitative categories: sweet, salty, sour, and bitter (Bartoshuk and Gent, 1985). It is not certain that all taste experience is described by those four adjectives (Erickson, 1985). Taste stimuli have also been described as alkaline or metallic, and recently, the "umami" taste, which is epitomized in the taste of monosodium glutamate, has been of interest (Lawless, 1987). The degree to which these additional sensations are pure tastes is currently under investigation. For example, it has been shown that the metallic "taste" of iron salt solutions disappears when the nose is clamped (Hettinger *et al.*, 1990).

Chemical characteristics (Figure 1) of natural sweet, salty, sour, and bitter stimuli have been defined (Moncrief, 1967), and molecular configurations have been synthesized that elicit tastes (Walters *et al.*, 1991) but do not have the physiological consequences of the natural stimulants. The sweet taste, associated primarily with caloric sources, is stimulated by chemicals with a number of hydrophilic molecular structures such as sugars, certain amino acids, and artificial sweeteners (e.g., saccharin and aspartame). The "pure" salty taste is elicited by sodium, an essential mineral, and lithium salts, but some potassium and ammonium salts are also salty. It has been very difficult to develop a non-sodium salty stimulus because lithium salts are toxic and non-sodium/lithium salts have a bitterness. Acids are sour, but dissociated hydronium ion concentration (pH) is not the sole determinant of sourness. The bitter taste, associated with poisons, is elicited by lipophilic compounds with diverse chemical structures, including alkaloids, thioureas, bile acids, and glycosides. Certain amino acids are also bitter. Many medications are bitter.

By far the majority of the physiological work on vertebrate taste systems has focused on understanding the sweet, salty, sour, and bitter tastes. In fact, it has been assumed that these four qualities are mediated by four relatively separate sensory submodalities. The finding that humans can detect sweetness, saltiness, sourness, and bitterness in mixtures (Batroshuk and Gent, 1985) is taken as evidence for their distinctiveness. Taste systems of a variety of terrestrial and aquatic vertebrates have been probed with taste stimuli that elicit four taste qualities in humans. Yet behavioral and physiological studies of carnivorous, omnivorous, and herbivorous terrestrial mammals suggest that each species' taste system

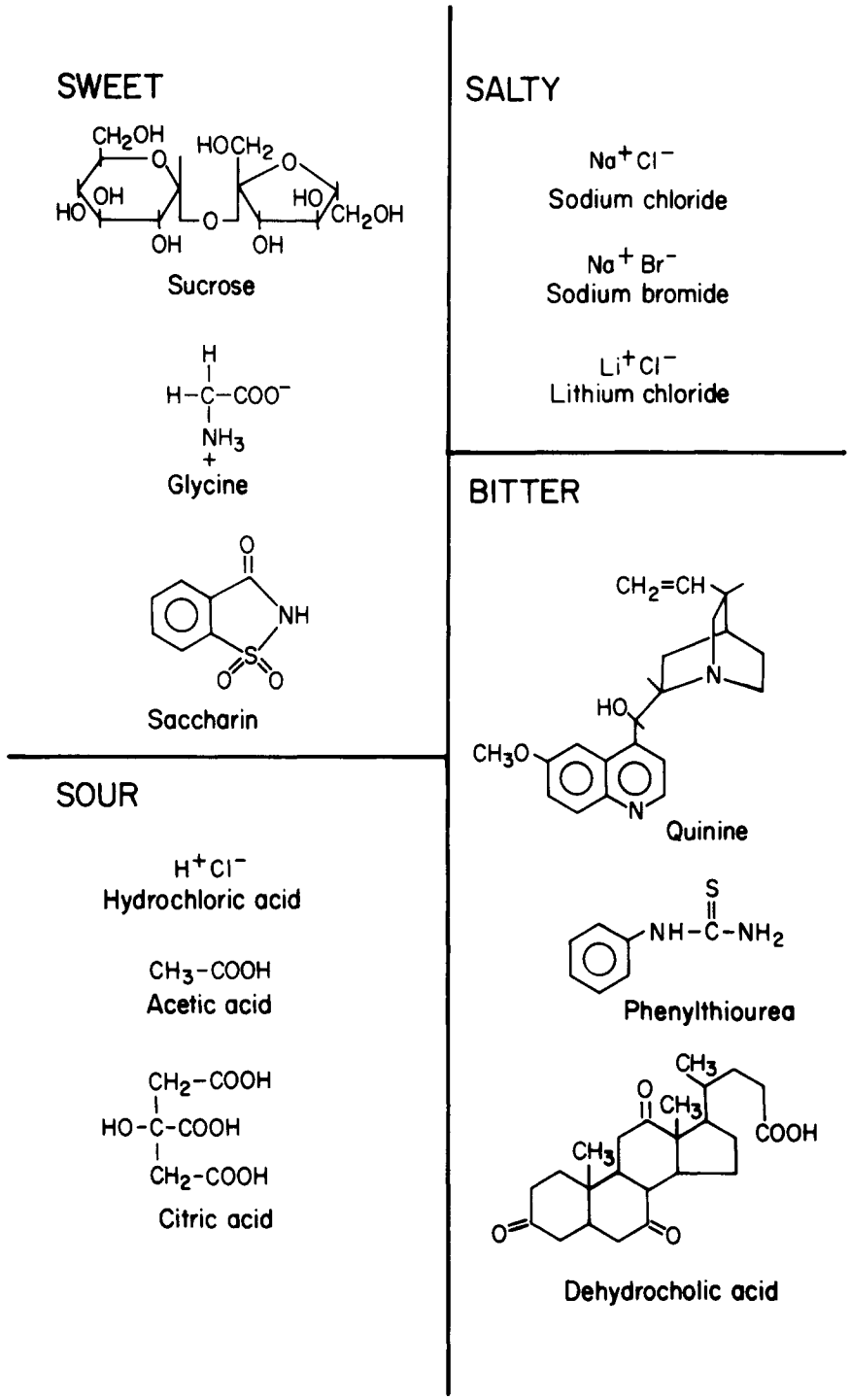

FIGURE 1. Chemicals that taste sweet, salty, sour, or bitter.

is in tune with the food sources for which it is specialized (Hellekant *et al.*, 1981; Boudreau *et al.*, 1985).

III. FIELDS OF TASTE RECEPTORS IN THE ORAL CAVITY

Taste receptors occur in taste buds that are found in four discrete fields within the human oral cavity. One field encompasses the dorsal and lateral surfaces of the anterior two thirds of the tongue. In this anterior lingual field, taste receptors are most concentrated at the tip of the tongue, and their numbers progressively fall off posteriorly and dorsally. In this field, taste buds are located superficially on the cup-shaped surfaces of connective tissue cores within the epithelium of mushroom-shaped fungiform papillae (Figure 2). More than half of the human fungiform papillae identified in cadaver material contain no taste buds (Miller and Bartoshuk, 1991). In one sample, three quarters of taste-bud-bearing papillae contained one to three taste buds, although a few papillae each contained more than a dozen taste buds (Arvidson, 1979).

The second oral taste field, the palatal field, lies in the stratified squamous and columnar epithelia covering the soft palate. The taste buds in this field have not been studied extensively, either structurally or physiologically. In several mammalian species, the numbers of taste buds in the palatal field approximate the numbers in the anterior lingual field (Travers *et al.*, 1987). Apparently, palatal taste buds are not associated with papillae of any form.

Taste receptors in the third and fourth oral fields are found below the tongue's surface within trenches of foliate and circumvallate papillae, respectively. In these posterior lingual fields, the great numbers of taste buds within the epithelium of the walls of the trenches are bathed with secretions of Von Ebner serous glands. The fleshy protrusions, called foliate papillae, are located at the lateral edge of the tongue immediately anterior to the palatoglossal arch and have varied

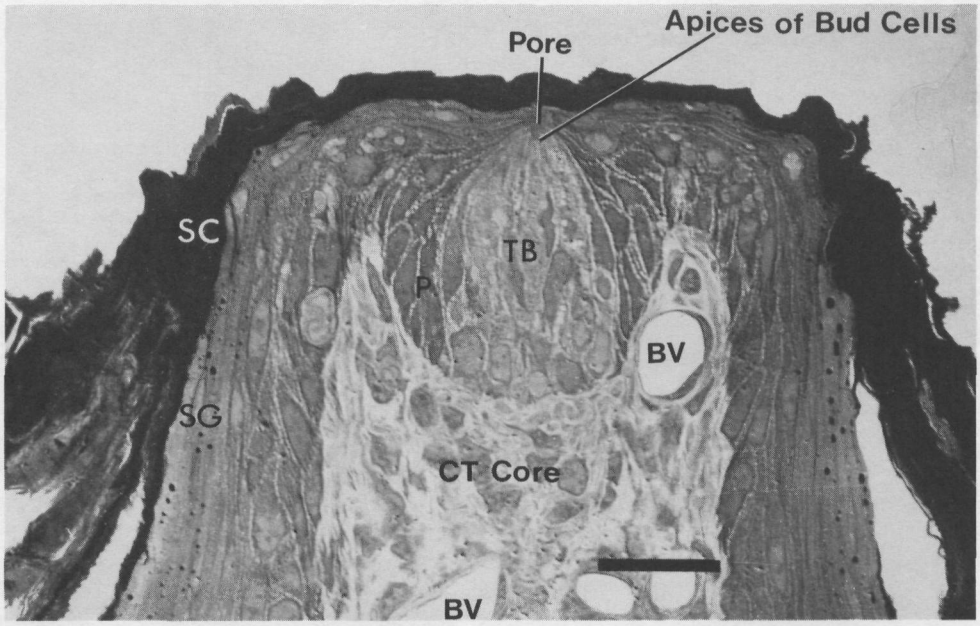

FIGURE 2. A section through the middle of a fungiform papilla of a golden hamster, showing a taste bud (TB), peripheral (P) cells, and the papilla connective tissue (CT) core. The taste pore (into which the apices of the taste-bud cell project), blood vessels (BV), stratum granulosum (SG), and stratum corneum (SC) are labeled. Bar = 20 μm. Stain = toluidine blue. (This figure is modified from Figure 1 in Whitehead *et al.* (1985). With permission.)

leaflike shapes. The more anterior lingual rugae (Hou-Jensen, 1933) have sometimes been mistaken for foliate papillae in humans. Each of the dozen circumvallate papillae has a circular appearance at the tongue's surface. Circumvallate papillae occur in a chevron-shaped pattern pointing posteriorly and define the posterior limit of the dorsal surface of the tongue. Thousands of taste buds occur on the walls of these papillae, which are surrounded by circular trenches. In addition to the oral fields, numerous taste buds are also found on the laryngeal side of the epiglottis. Epiglottal taste buds are thought to primarily sense chemicals in order to protect the airway, and they may not contribute to taste perception (Smith and Hanamori, 1991).

The loci of oral taste fields suggest that their chemoreceptor populations serve different functions. In the anterior lingual and palatal fields, groups of a few superficial taste buds are distributed over an expansive epithelial surface, albeit with varying density. In the posterior lingual fields, however, many taste buds are confined to trenches well below the surface of the tongue. In fishes, anterior taste buds, most of which are on the external body surface, appear to be involved in locating and identifying nutrients. Taste buds within the posterior oral cavity appear to implement swallowing or rejection of food items (Atema, 1971; Finger, 1987).

Although the several oral receptive fields may play different roles, taste function in humans is frequently studied as a "whole-mouth" sense (Bartoshuk, 1989a; Schiffman *et al.*, 1990). Subjects sample taste solutions from cups and are given instructions to distribute the solutions over all oral taste-bud fields. Recent studies that assess function in the different taste fields separately (Bartoshuk, 1989b) should determine whether the information provided is redundant. In whole-mouth tests, samples of young people ascribe greater intensities to their taste sensations (after correcting for responses to water) than samples of aged people (Figure 3). Aged people apparently attribute a stronger taste to water than young people do. Particularly noteworthy is that a tenfold increase in stimulus concentration is accompanied by, on the average, a 3.7-fold increase in taste intensity for the aged, compared with a 5.9-fold increase for the young. Thus, although some aged individuals rate tastes as strong as young people, tastes are less distinct for the aged than the young, with concentration differences not as clear.

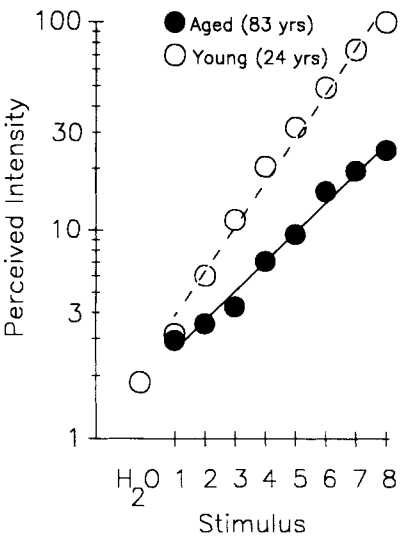

FIGURE 3. The perceived taste intensity of a concentration series of sucrose, NaCl, citric acid, and quinine·HCl solutions in young and aged adults. Separate data for the four compounds, given in Bartoshuk *et al.* (1986), were averaged. The taste intensity given to water was equated for the young and aged. The concentration at which a clear increment above the taste intensity ascribed to water (mean for young: 1.9, as shown; mean for elderly: 7.1) was designated stimulus 1. The next seven higher concentrations were designated stimuli 2 through 8. Concentrations were tested at one fourth log steps between 0.018 and 1.0 *M* sucrose; 0.01 and 0.56 *M* NaCl; 0.1 and 5.6 m*M* citric acid; and 0.01 and 0.56 m*M* quinine·HCl. The mean magnitude estimate for each stimulus was plotted for the 18 aged (mean age, 83 years) and 18 young (mean age, 24 years) adults. A least-squares fit yielded the straight lines shown, which are good fits to the data points (r^2 = 0.986 [young] and 0.985 [aged]).

IV. THE TASTE BUD

After routine staining, microscopic taste buds (50 to 200 μm in diameter) are seen easily (Figure 2) in epithelial fields where taste can be elicited. They are trophically maintained by primary afferent neurons in adult vertebrates (Oakley, 1985), although taste-bud "anlage" remain in fungiform papillae after nerve section (Whitehead *et al.*, 1987; Barry and Frank, 1992). Taste buds

are comprised of 50 to 100 cells that form a distinct spherical organ that is grossly similar in all vertebrate taste fields. The majority of the cells are spindle shaped, having long axes oriented toward the surface of the epithelium and basal lamina. The apices of the cells protrude above the surface of the epithelium into a taste pore that contains mucus. Several types of cells are seen with the electron microscope (Kinnamon, 1987). Cells with dark cytoplasm are more likely to be located around the periphery of the bud, and cells with light cytoplasm near its center. Tight junctions tie apical membranes of bud cells together. Dark cells are most numerous, contain secretory granules, may be coupled via gap junctions, and show surface microvilli. They are thought to play a supporting and/or secretory role. Light cells are much less numerous; they contain extensive smooth endoplasmic reticulum, and some possess an apical clublike protrusion that extends to the surface of the mucus. Light cells are thought to be the cells that are directly involved in the transduction of taste stimuli. Spherical basal cells, seen at the base of taste buds in posterior lingual fields, represent a small percentage of the cells in the bud. These cells are thought to be stem cells for the continually generating mammalian taste bud. Stem cells are thought to surround the periphery of buds within anterior lingual taste fields (Figure 2).

Taste-bud cells turn over at a fairly rapid rate in mammals (Beidler and Smallman, 1965). Autoradiographic studies of the distribution of silver grains after injection of tritiated thymidine indicate a life span of 10 d. The number of stem cell populations from which the mature taste bud derives is a matter of debate (Delay *et al.*, 1986). Some propose that the different cell types in the bud form sequentially from one cell line; others suspect that dark and light cells are generated from different cell lines (Farbman, 1980). Observations of but a few taste-bud cells undergoing mitosis have not been helpful in this matter. A rapid turnover of the taste-bud cell population is considered a problem for the stable transmission of information about taste to the brain. However, turnover does provide the potential for a rapid recovery from injury if the stem cells are preserved (Barry and Frank, 1992; Sato and Kamata, 1984).

Antineoplastic drugs (Table 1) have been associated with taste losses, especially at high doses (Schiller *et al.*, 1989). For example, electrogustometric thresholds were elevated in 5 of 50 patients treated weekly with bleomycin for 5 weeks (Soni and Chatterji, 1985). Taste loss was first observed in the second week of chemotherapy and was reversed 10 to 12 weeks after chemotherapy was discontinued. The effects of cytotoxic drugs on the taste system has been associated with normal rapid turnover of the taste-bud receptor cells. Taste losses, however, may also be secondary to salivary gland injury, which clearly affects taste-mediated behaviors in animals (Brosvic and Hoey, 1990; Catalanotto *et al.*, 1986).

The basolateral membranes of taste receptor cells may be specialized for direct synaptic transmission to innervating primary afferents. In electron micrographs, many primary afferent nerve endings are seen within taste buds, particularly near the cell nucleus. However, clear morphological evidence for typical excitatory synapses is not commonly observed. In fact, in aquatic vertebrates, synaptic specializations are more often seen between bud cells than between a bud cell and nerve ending. The taste bud may not be as simple a sensory end organ as it has been commonly thought to be. It may contain networks of interacting cells that process taste information before transmission to nerve endings (Roper, 1989). This possibility might help explain the differences between electric taste stimulation and chemical taste stimulation (Ninomiya *et al.*, 1987 and 1989). The anodal electrical stimulus may bypass some of the circuitry of the bud (Herness, 1988; Frank and Smith, 1991). The effect of aging on taste has been attributed to a decline in the numbers of taste buds in the oral cavity. However, more recent evidence from nonhuman (primate: Bradley *et al.*, 1985; rat: Mistretta and Oakley, 1986) and human material (Miller, 1988) suggests that the numbers of taste buds in aged and young individuals differ slightly (Mistretta, 1989). For example, in long-lived rats, those older than 30 months had about 10% fewer fungiform taste buds than those younger than 6 months (Mistretta and Oakley, 1986). In rats it is relatively easy to count taste buds in fungiform papillae, because one bud is found in each papilla

TABLE 1
Some Medications Associated with Taste Intensity Change

Type	Name	Dose[a]	Ref.
Antiarthritic	Penicillamine	250 mg	Keiser
Antihypertensive	Captopril	104 mg, 266 mg	Abu-Hamdan
	Amiloride	10 mg	Mattes
Antineoplastic	Cisplatin	198 mg	Schiller
	Bleomycin	—	Soni

[a] Daily doses are given for penicillamine, captopril (group averages), cisplatin, and amiloride; dose information for bleomycin was not included.

and the fungiform are easily distinguished from the taste-budless filiform epithelial spikes. In humans, however, it is much more difficult to distinguish between papilla types, given the varied topography of the anterior human tongue (Miller and Bartoshuk, 1991). This difficulty may contribute to the variability reported on human fungiform taste-bud numbers (Arvidson, 1979). The number of taste buds identified on the tip of the tongue varied widely in material from five people who died at younger than 50 years (4–170, median 130 taste buds) and five people who died at older than 70 (21–150, median 50 taste buds). With such within-age-group variation, it would be difficult to verify an average 10% loss in taste-bud numbers with aging (Miller, 1989).

V. TRANSDUCTION OF TASTE STIMULI

It is generally assumed that there is more than one mechanism of transduction (Kinnamon, 1988; Avenet and Kinnamon, 1991) for chemicals that taste (Moncrieff, 1967). Taste stimuli can be broadly divided into ionic and nonionic varieties (Figure 1). Transduction of ionic taste stimuli is thought to involve ion channels directly, whereas transduction of hydrophilic nonionic taste stimuli may require binding to membrane-bound, proteinaceous receptors and transduction of lipophilic nonionic taste stimuli may include their dissolving into the lipid bilayer of the membrane (Teeter and Brand, 1987). Typically, transduction mechanisms for sweet, salty, sour, and bitter stimuli are studied separately, although it is recognized that there may be more than one mechanism for each taste quality (Jakinovich and Sugarman, 1988). Chemical structures that elicit the sweet quality, for example, are varied (Figure 1) and may not all interact with the same molecular receptor. Studies of cellular events that are the bases for taste transduction are impaired by the difficulty in attributing roles to the types of taste-bud cells and the small size of the cells.

Traditional biochemical isolation and binding studies have attempted to identify membrane-bound, proteinaceous receptors for sweet taste in mammals and "amino acid" taste in catfish (Teeter and Brand, 1987). Studies of sweet-binding proteins have been hampered because most natural sweet stimuli show weak binding (half-saturation near 100 m*M*). Current evidence suggests that cyclic nucleotides act as intracellular second messengers for sweet transduction (Teeter and Gold, 1988). Amino acid taste stimuli for catfish (Caprio, 1978) have effects that suggest stronger binding (half-saturation at micromolar levels). "Amino-acid-binding" glycoproteins have been isolated from catfish barbels and partially characterized (Teeter and Brand, 1987). Amino acids are sweet/bitter to humans. The sweet taste does appear to diminish with aging in humans (Schiffman *et al.*, 1981; Moore *et al.*, 1982), although to a lesser degree than the salty, sour, and bitter tastes (Weiffenbach, 1987). In fact, neurophysiological recordings from the chorda tympani nerve in old long-lived rats suggest that the responses to the sweet stimulus sucrose are relatively preserved with aging in comparison to responses to salty sodium chloride (McBride and Mistretta, 1986).

Proteins that specifically bind bitter compounds such as quinine (half-saturation at micromolar levels) have not been found. The di-

verse lipophilic chemicals that are bitter and their 1-million-fold effective ranges indicate that they may be having general effects on taste cell membranes. A release of calcium from intracellular stores following bitter stimulus reception suggests an inositol phospholipid pathway in bitter transduction (Akabas *et al.*, 1988). Although perceived intensities of high concentrations of chemicals of all taste qualities may be reduced in the aged (Schiffman *et al.*, 1981; Weiffenbach, 1987), it is the bitter taste that is most affected (Murphy and Gilmore, 1989; Weiffenbach *et al.*, 1986; Bartoshuk *et al.*, 1986), as can be seen in Figure 4. Weiffenbach *et al.* (1986) report that the intensity of strong quinine is estimated to be about 40% less intense in the elderly, whereas strong sucrose intensity is slightly reduced. This differential bitter loss is also seen for caffeine (Murphy and Gilmore, 1989; Gilmore and Murphy, 1989), although caffeine and quinine bitter sensitivities are not always linked in humans (Hall *et al.*, 1975).

Acids may taste sour because hydrogen ions enter taste receptor cells and inactivate voltage-dependent potassium channels during stimulus transduction (Kinnamon and Roper, 1988). The relevant potassium channels appear to be concentrated in the apical membrane, where stimuli interact with the cell membrane (Kinnamon *et al.*, 1988). However, ionic stimuli could also have paracellular effects (Harper, 1987; Elliott and Simon, 1990; Ye *et al.*, 1991). The intensity of sour-tasting acids is reduced with aging but less than the bitter taste (Murphy and Gilmore, 1989; Weiffenbach *et al.*, 1986; Figure 4). In electrogustometry, which is useful in identifying losses in ionic taste perception (Frank and Smith, 1991), small anodal currents (1 to 100 μA) are applied to the tongue, resulting in a sour-metallic taste. The average electrogustometric threshold increases from about 10 to about 60 μA from age 15 to age 65 (Krarup, 1958; Figure 5).

Ionic sodium-salt taste stimuli may directly enter taste cells through ion channels, carrying currents of transduction. Transepithelial currents have been observed across mammalian lingual epithelia that correlate with neural responses of afferent neurons to sodium salts (DeSimone *et al.*, 1984). When applied to the tongue, amiloride, an epithelial ion-channel blocker and diuretic

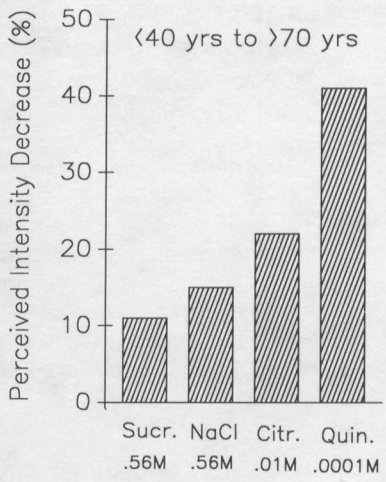

FIGURE 4. The percentages of decrease in perceived intensity of strong sweet (0.56 *M* sucrose), salty (0.56 *M* NaCl), sour (0.01 *M* citric acid), and bitter (0.0001 *M* quinine$_2 \cdot H_2SO_4$) taste stimuli in aged compared with young adults. Taste intensity judgments made by 44 people between 22 and 39 years old (<40 years) and 44 people over 70 years old (>70) were reported by Weiffenbach *et al.* (1986). The data are expressed as percentages of decrease.

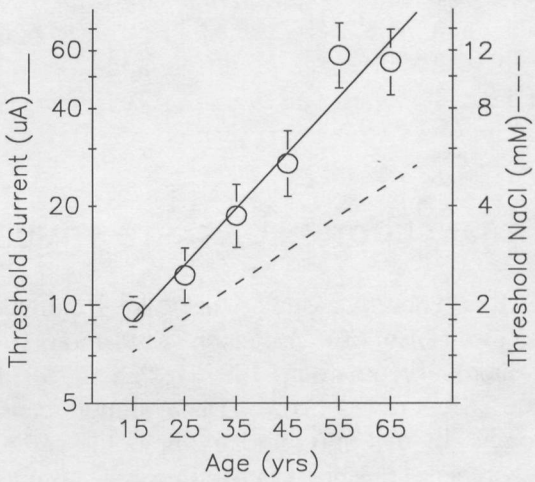

FIGURE 5. Threshold for anodal current (μA) applied to the surface of the anterior tongue with a 5-mm-diameter stainless steel electrode as a function of age. The ages are midpoints of 10 years for groups containing 20 people each. The points are means and standard errors for data given in Krarup (1958). A least-squares fit is shown by the solid straight line. For comparison, the effect of age on threshold for NaCl (m*M*) is indicated by a dashed line, established with data presented in Weiffenbach *et al.* (1982) for 81 people ranging in age from 23 to 88 years. Electric taste and NaCl thresholds increase progressively with age.

utilized in the treatment of hypertension, drastically reduces transepithelial currents and responses of taste neurons that are specific for sodium/lithium salts (Ninomiya and Funakoshi, 1988) at micromolar concentrations (Hettinger and Frank, 1990). When ingested at therapeutic doses (Table 1), amiloride does not appear in the saliva. However, within 2 weeks, amiloride results in reduced salivary sodium levels and a reliable decrease in NaCl taste recognition threshold (9 to 6 m*M*), which persist for an 8-week medication period (Mattes *et al.*, 1988). As with other drugs that affect taste through a systemic route (Rollin, 1978), taste thresholds return to normal within 3 weeks. Thus, systemic amiloride increases NaCl sensitivity, presumably by decreasing salivary sodium levels with its diuretic properties. However, direct application of amiloride to the tongue decreases NaCl taste responses by blocking a sodium channel necessary for salt-taste transduction (Schiffman *et al.*, 1983 and 1986).

A topical medication that profoundly affects the ability to appreciate the salty taste of NaCl is chlorhexidine gluconate when used as a mouthwash for removal of dental plaque (Lang *et al.*, 1988; Frank and Smith, 1991; Helms and Frank, 1989). Rinsing with prescribed chlorhexidine solutions profoundly reduces the perceived intensity of sodium chloride and quinine hydrochloride solutions (Figure 6). It has no significant effect on the tastes of citric acid or sucrose solutions. Chlorhexidine effects are reversible after termination of medication. Effects of chlorhexidine on salt and bitter taste may be independent. Sodium salt transduction likely involves ion channels that exist primarily on the anterior tongue (Formaker and Hill, 1991), and bitter transduction involves effects of lipophilic stimuli on cell membranes, which occur primarily on the posterior tongue in rodents (Frank, 1991). Evidence suggests that chlorhexidine binds strongly to tissue, remaining for many hours after application, and its effects include making bacterial cell membranes "leaky" (Gardner and Gray, 1983).

Aging has an effect on sodium-salt detection in humans (Grzegorczyk *et al.*, 1979; Weiffenbach *et al.*, 1982; Schiffman *et al.*, 1990), with a gradual tripling of the average NaCl threshold concentration (0.002 to 0.006 *M*) occurring from 15 to 65 years of age (Figure 5). A much higher NaCl threshold (0.02 *M*) is seen in 75 year olds (Schiffman *et al.*, 1990). The variability in measured taste thresholds at any age is often quite large (Bartoshuk *et al.*, 1986), requiring the testing of many subjects with sensitive methods (Weiffenbach, 1987) to define a trend.

The differential effects of aging on sensations of different taste quality, with bitter affected the most and sweet the least, suggest that the distinct cellular mechanisms of taste transduction are differentially affected by aging (Murphy and Gilmore, 1989). It seems less likely that an aging effect on the processing of taste information by the central nervous system would affect bitter perception more than sweet. It is also unlikely that cognitive difficulties of the elderly would affect perception of one taste quality more than another. Thus, clues to the effects of age on taste may come from a greater understanding of the differences between the transduction of sweet hydrophilic stimuli and bitter lipophilic stimuli.

Intracellular electrophysiological recording from mammalian taste-bud cells *in vivo* has proven to be difficult. The sparse data suggest that individual taste cells are not specialized for chemicals of one taste quality. The nonspecificity could reflect difficulties in recording intracellularly from small cells. Alternatively, it is possible that each cell type in the bud plays a specialized undefined role in the process (Roper, 1989) that may not be directly associated with taste quality. Studies on aquatic vertebrates suggest that different populations of cells play distinct transductory roles. For example, one class of frog taste cell depolarizes but another hyperpolarizes to NaCl (Sato and Beidler, 1975). In the mud puppy, the relatively large taste-bud cells respond to injected current with a single action potential. The action potential is blocked by tetrodotoxin, which implies it is mediated by voltage-gated sodium channels (Kinnamon and Roper, 1987) and suggests that the membranes of some taste-bud cells have active, neural properties (Avenet and Kin-

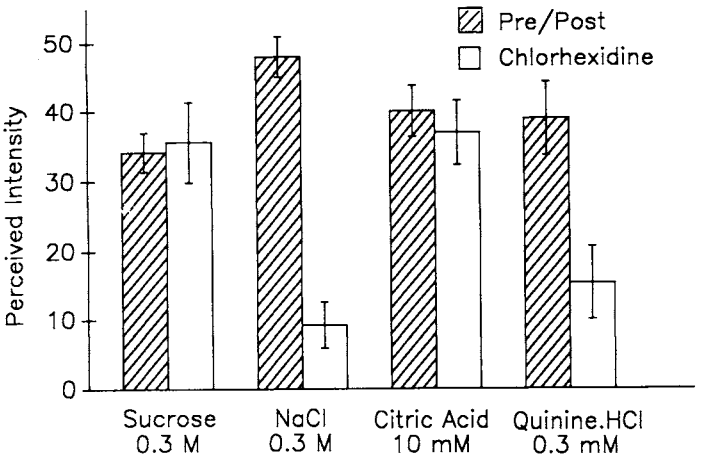

FIGURE 6. The effect of chlorhexidine mouthwash on the perceived intensities of sweet (0.3 *M* sucrose), salty (0.3 *M* NaCl), sour (10 m*M* citric acid), and bitter (0.3 m*M* quinine·HCl) stimuli. Ten subjects rated the magnitudes of taste solutions days before, days after (pre/post: average plotted), and during (chlorhexidine: 30 min subsequent to a fourth daily morning rinse) applications of 0.12% chlorhexidine gluconate solutions. Intensities of sucrose and citric acid were not affected, but intensities of NaCl and quinine were (*t* tests, $p < 0.01$). (These data are from a study reported by Helms and Frank (1989).)

namon, 1991), although amiloride sensitivity of salt reception suggests that some taste-bud cells have passive, epithelial properties.

VI. PRIMARY TASTE AFFERENT NEURONS

Taste buds are innervated by sensory afferent relay neurons. The different taste fields are served by branches of the facial (VIIth), glossopharyngeal (IXth), and vagus (Xth) cranial nerves. Soma of the pseudo-unipolar sensory neurons lie in the geniculate, petrosal, and nodose cranial ganglia for nerves VII, IX, and X, respectively. The anterior lingual taste field is innervated by the chorda tympani nerve. The palatal field is innervated by the greater superficial petrosal nerve. These nerves are branches of the facial nerve. The posterior lingual fields are innervated by the lingual branch of the glossopharyngeal nerve. Epiglottal taste buds are innervated by the superior laryngeal branch of the vagus nerve.

Electrophysiological recordings from terrestrial and aquatic vertebrates show that the facial taste fields are most sensitive to sweet, salty (Frank *et al.*, 1988; Frank *et al.*, 1983; Nejad, 1986), and amino-acid stimuli (Caprio, 1988). The glossopharyngeal fields are most sensitive to bitter and sour stimuli (Frank, 1991; Hanamori *et al.*, 1988). The epiglottal field responds poorly to nonionic taste stimuli but responds vigorously to ionic stimuli and water (Smith and Hanamori, 1991; Bradley *et al.*, 1983). Cross-reinnervation studies in adult rodents in which the nerves are forced to grow to foreign fields show that taste sensibilities reside in taste-bud receptors and do not change with the source of afferent innervation (Oakley, 1985).

Sensory axons outnumber taste buds in rodents by four to one for the anterior lingual field (Beidler, 1969). Furthermore, as many as a dozen taste buds provide input to a single chorda tympani neuron (Miller, 1971; Pfaffmann, 1970). Thus, an average taste afferent nerve fiber gathers input from a number of taste buds, and a taste bud is providing input to a number of different neurons. Nonetheless, populations of taste afferents in the chorda tympani nerve show similar response spectra (Figure 7). Also, indistinguish-

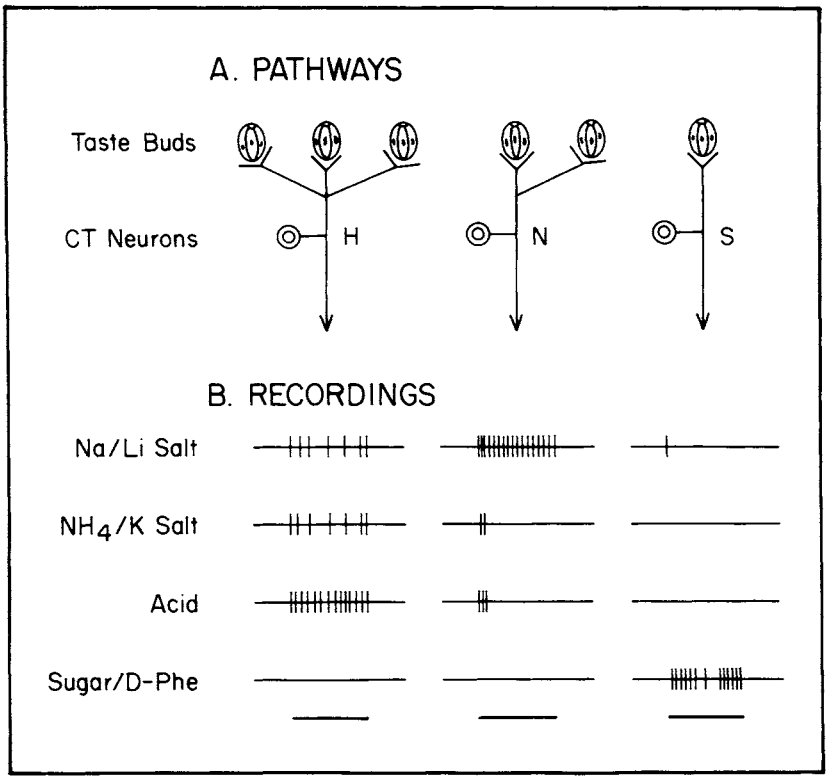

FIGURE 7. Response spectra of chorda tympani (CT) generalist (H) and specialist (N, S) afferents. Populations of primary neurons are responsive to ionic stimuli, or Na/Li salts, or sugars and "sweet" amino acids. The bars beneath the recordings indicate a 3-s stimulation period, and the short vertical lines in the recordings mark occurrences of nerve impulses. (This figure is based on data presented in Frank *et al.* (1988).)

able response spectra are seen when separate parts of the receptive field of a neuron are stimulated independently (Oakley, 1975). The number of fungiform papillae comprising receptive fields (Nagai *et al.*, 1988) and the location of the receptive fields (Boudreau *et al.*, 1985) differ for neurons with different chemical sensibilities. These findings suggest that a primary taste afferent gathers similar information from every part of its characteristic receptive field.

The set of chemicals that activate chorda tympani neurons differs across species. For example, the chorda tympani nerve of the herbivorous golden hamster is composed of specialist neurons that selectively respond to sugars or sodium/lithium salts and generalist neurons that respond to a wide spectrum of ionic stimuli (Frank *et al.*, 1988; Figure 7). In contrast, populations of neurons in the facial nerve of the carnivorous cat respond primarily to certain amino acids (e.g., L-cysteine, L-proline, L-histidine, L-lysine) or Bronsted acids (Boudreau *et al.*, 1985). The spectrum of chemicals to which an individual generalist taste-afferent responds includes chemicals differing in taste quality. For example, ionic generalist neurons of hamsters respond to NaCl, which has a unique taste to hamsters (Nowlis *et al.*, 1980; Frank and Nowlis, 1989), as well as many other ionic stimuli that do not taste like NaCl (e.g., KCl, HCl). Specialist taste neurons appear to detect essential chemical features that are likely to be encountered in the food sources of the species. For example, the Na/Li specialist chorda tympani neurons detect an essential mineral (sodium) that is transduced via a passive sodium channel that is blocked by amiloride (see above).

The responsiveness of the Na/Li detectors can be reversibly affected by dietary constraints such as a low-sodium diet in adults (Contreras

and Frank, 1979), as well as irreversibly during earlier, critical periods in ontogeny (Hill, 1987). Na/Li-sensitive neurons develop more slowly than other taste afferents in some mammalian species, and their development is associated with a decrease in receptive field size (Nagai *et al.*, 1988). The information that the primary afferent taste neurons relay to the brain stem is not fixed from birth but develops with age and is sensitive to nutritional constraints.

VII. TASTE IN THE BRAIN STEM: NUCLEUS OF THE SOLITARY TRACT

Primary afferent neurons for taste project ipsilaterally to the rostrolateral portion of the nucleus of the solitary tract (Hamilton and Norgren, 1984), which also receives general visceral sensory projections, mediocaudally (Contreras *et al.*, 1982; Figure 8). This nucleus extends through most of the dorsal medulla oblongata. The intermediate nerve, containing the centrally projecting axons of chorda tympani and greater superficial petrosal neurons with soma in the geniculate ganglion, enters the solitary tract most rostrally. Glossopharyngeal and vagal afferents enter the tract in sequence, more caudally. Taste afferent axons run rostrocaudally in the solitary tract, exiting to end on dendritic processes in the adjacent central and lateral divisions of the nucleus (Whitehead and Frank, 1983; Whitehead, 1988). Oral trigeminal afferents, which process general sensory (e.g., thermal, mechanical) stimuli for the anterior tongue, also project to the solitary nucleus. Their projection site is more caudal than taste projection for the anterior tongue (Contreras *et al.*, 1982). Taste projections are topographic, but there is considerable overlap. Anterior tongue and palatal taste fields are represented most rostrally; representations of posterior lingual and epiglottal fields are more caudal. In some primates, taste afferent axons terminate in a rostral extension of the nucleus (Beckstead and Norgren, 1979), anterior to the point of entry of the intermediate nerve and the beginning of the solitary tract (Norgren, 1984).

The organization of the taste portion of the mammalian nucleus of the solitary tract is difficult to study because it is small and borders that separate it from visceral portions of the solitary nucleus are not clear. However, the facial lobe, a homologous structure, is a dorsal extension of the medulla seen in certain fishes that are highly specialized for taste (Finger, 1987). This "hypertrophied" taste nucleus is somatotopically organized, with the representation of each cutaneous taste field segregated in a separate lobule. In some fish, neurons that respond to taste stimuli rim the surface of a lobule, and neurons more deeply located respond to mechanical stimulation of the same field (Hayama and Caprio, 1989). The representations of chemical and mechanical stimuli for the same cutaneous fields are apposed to one another.

As noted above, individual primary taste afferent neurons receive input from several taste buds, but that convergent input is highly organized. Information regarding chemical features is transmitted to the brain stem over separate neural populations (see above). Recordings from secondary taste neurons in the solitary nucleus indicate that they also receive convergent input. First, individual brain stem neurons typically respond to more stimulus categories than do the primary afferent neurons (Travers *et al.*, 1987). Second, receptive fields are about four times larger for taste neurons in the solitary nucleus than those for primary afferent neurons (Vogt and Mistretta, 1990). Third, about half of the neurons recorded in the rat solitary nucleus receive input from several oral taste fields (Travers *et al.*, 1986). The convergence is typically for inputs from the anterior lingual taste field, via the chorda tympani nerve, and a taste field that lies directly above it on the rat's palate, via the greater superficial petrosal nerve (Figure 9). Some of the brain stem neurons respond to the same stimulus category on the two separate taste fields. Others, however, are stimulated by salt on the tongue and sugar on the palate. The pattern of convergence may relate to the site to which the recorded neuron projects. For example, field- and stimulus-specific neurons may project forward to the thalamus, whereas field- and stimulus-convergent taste neurons may project downstream. Many neurons in the nucleus project downstream to motor nuclei in the brain stem (Ogawa *et al.*, 1984; Travers, 1988).

In spite of convergence of afferent inputs onto brain stem taste neurons in the solitary nucleus, distinct roles for different taste-bud fields

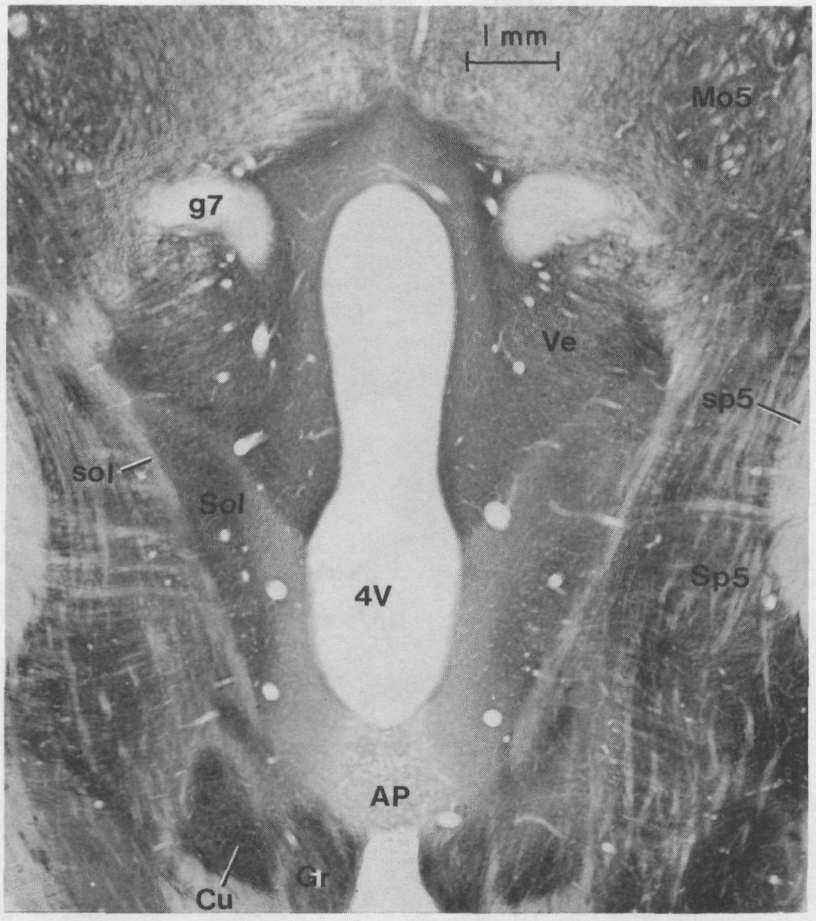

FIGURE 8. A horizontal section through the dorsal medulla of the golden hamster, showing the nucleus of the solitary tract (Sol) and the surrounding brain stem (rostral is up, caudal down). The cytochrome oxidase mitochondrial staining is darkest where many afferent endings are located. The rostral pole of the solitary nucleus, where taste activity is recorded, is dark, as is the entire lateral division of the nucleus (seen most clearly on the right). The rostral pole is about 0.5 mm^3 in the hamster. Fiber tracts such as the solitary tract (sol), the spinal trigeminal tract (Sp5), and the genu of the facial nerve (g7) do not stain. The cuneate (Cu) and gracile (Gr) nuclei are also labeled on the left. The fourth ventricle (4V) and area postrema (AP) are labeled at the midline; and the motor trigeminal (Mo5), spinal trigeminal (Sp5), and vestibular (Ve) nuclei are labeled on the right. The clear ovoids are blood vessels. (This section was provided by M. McPheeters.)

(Travers and Norgren, 1991) and specific afferent types (Giza and Scott, 1991; Jacobs *et al.*, 1988) appear to be preserved or even enhanced (Scott and Giza, 1990) in the brain stem. In addition, the effects of forebrain-mediated learning, which can change a stimulus from positive to negative, are accompanied by changes in response patterns of neurons in the solitary nucleus (Chang and Scott, 1984). Thus, as the convergence of taste buds onto peripheral afferents is highly organized, so are ascending influences from different taste-bud fields and descending influences from higher levels of the nervous system onto brain stem taste neurons. Besides relaying sensory information about sweet, salty, sour, and bitter to the forebrain, the nucleus of the solitary tract is involved in the integration of taste-mediated reflexes (Travers *et al.*, 1987).

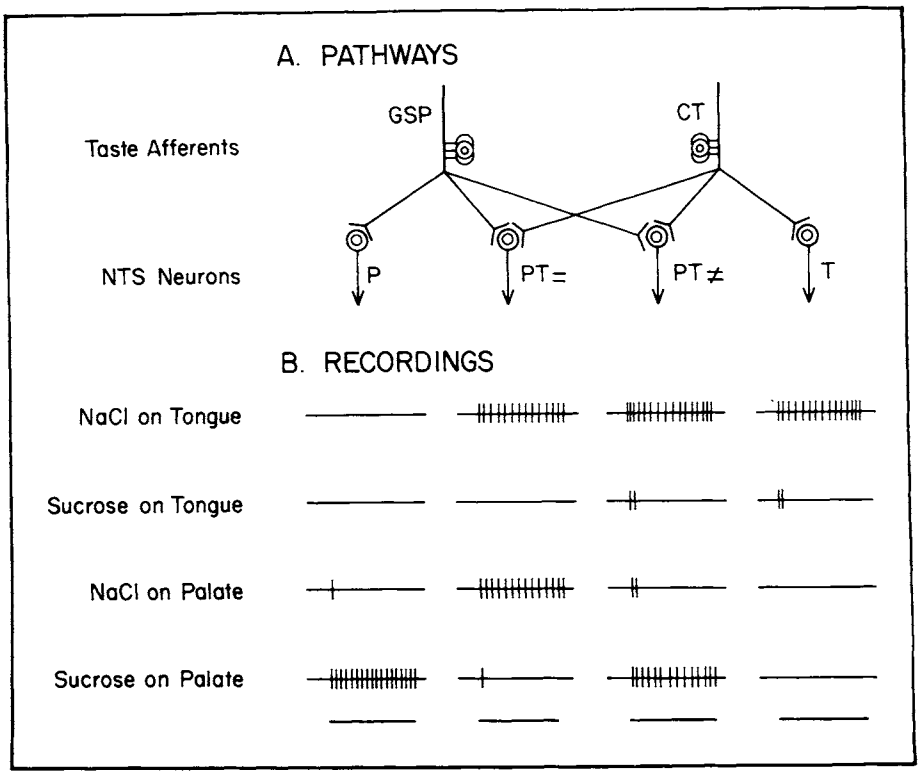

FIGURE 9. Convergence of taste information from different taste fields via the greater superficial petrosal (GSP) and chorda tympani (CT) nerves on neurons in the nucleus of the solitary tract (NTS). Recordings are from NTS neurons. About half of the NTS neurons respond to stimulation of either the palate (P) or the anterior tongue (T). However, the other half respond to stimulation of palate and tongue (PT). Recordings from the convergent neurons show that they respond either to the same stimulus (PT=) or to different stimuli (PT≠) on the two taste fields. (This figure is based on data presented in Travers *et al.* (1986).)

The solitary nucleus is the first central nucleus for taste in all mammals yet investigated. However, the second central taste nucleus is in the brain stem in rodents (Norgren and Leonard, 1973) but in the forebrain in primates (Beckstead *et al.*, 1980). In rodents, the special sense of taste and general visceral (interoceptive) sensory systems both project upstream a short distance from the solitary nucleus to parabrachial nuclei in the pons. The taste projection to the parabrachial nucleus is primarily to the central medial region, but there is also a small projection to the ventral lateral region (Halsell and Frank, 1991) that has been implicated in general visceral function (Cechetto, 1987). This latter region could allow for interactions between taste and general visceral inputs required for the learning of conditioned taste aversions (see below). Taste and visceral portions of the parabrachial nucleus project to the thalamus as well as ventral forebrain structures such as the amygdala and hypothalamus (Halsell, 1992). Taste-responsive neurons in the parabrachial nucleus fall into relatively congruent classes that are involved in detecting sweet stimuli and sodium salts, but there is controversy about their detection of sour-bitter stimuli (Smith *et al.*, 1983; Travers and Smith, 1984; Nishijo and Norgren, 1990). In primates, cells in a general visceral portion of the solitary nucleus project to pontine parabrachial nuclei, whereas cells in a gustatory part of the solitary nucleus project directly to the thalamus (Figure 10).

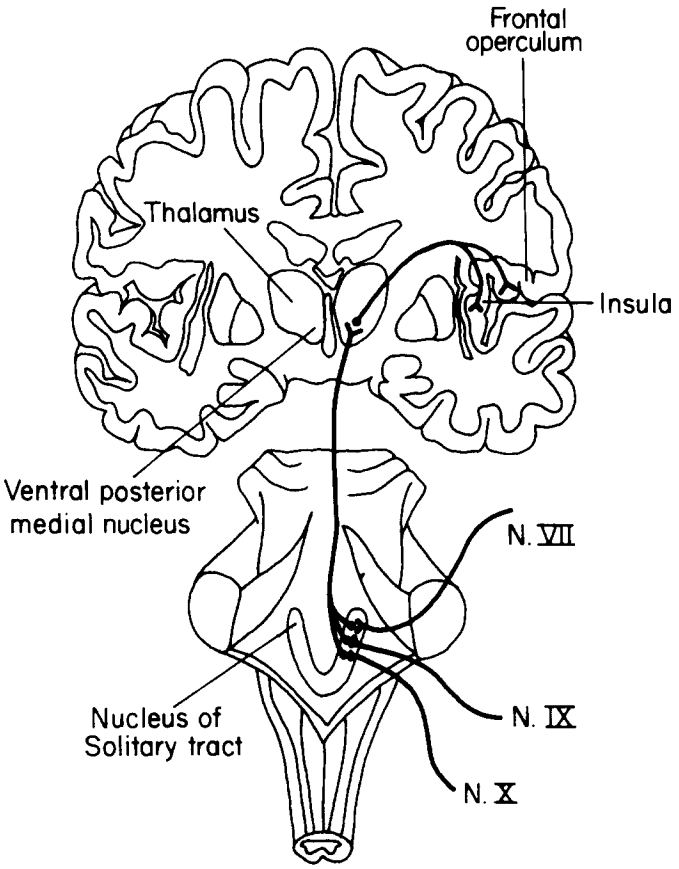

FIGURE 10. Central taste projections superimposed on a drawing of a dorsal view of the brain stem and a coronal section of the forebrain. (This figure was derived from figure 34–14 in Dodd and Castellucci (1991).)

VIII. TASTE IN THE FOREBRAIN: VENTRAL POSTEROMEDIAL THALAMIC NUCLEUS AND OPERCULAR/INSULAR CEREBRAL CORTEX

The parts of the mammalian forebrain that have been identified as components of the primary afferent taste pathway lie close to the general somatic sensory areas specific for the tongue epithelium (Finger, 1987). The thalamic taste area, a parvicellular division of the ventral posteromedial nucleus in primates, is adjacent and medial to the somatosensory lingual representation (Beckstead *et al.*, 1980). It is at this level where taste representations become bilateral in mammals, although the ipsilateral projection appears to be much stronger in primates. Portions of the thalamic gustatory representations are separate from lingual general sensory representations, but there is overlap. The anterior lingual taste field is represented rostral to the posterior lingual field, as it is in the brain stem. Thus, the taste projections remain grossly somatotopically organized to this level.

Physiological studies of the thalamic taste area have been especially sparse. Thalamic taste neurons appear to have somewhat more complex response properties than do brain stem taste neurons or primary taste afferents. About half of these thalamic neurons respond rather specifically to stimuli of one taste quality, with the great majority most sensitive to either sweet sucrose or salty NaCl. Few thalamic taste-responsive neurons respond to negative bitter-sour stimuli, which contrasts with solitary nucleus neurons also recorded in alert primates (Scott *et al.*, 1986).

The other half of the neurons in the same thalamic taste region show patterns of inhibition, "anticipating" presentation of taste stimuli (Pritchard *et al.*, 1989). Thus, the primary forebrain relay for taste in primates introduces complexity in response properties of neurons not seen in the brain stem, suggesting a role in sensory-motor integration of ingestive behavior.

Similar to the thalamic taste representation, primary taste cortex is located near the lingual somatosensory representation. In gyrencephalic primates, taste cerebral cortex is buried within the invaginated frontal operculum and contiguous anterior insula (Pritchard *et al.*, 1986; Figure 10). In lissencephalic rodents, primary taste cortex is found ventral to lingual somatosensory representations in insular cortex, immediately below the representation for lingual temperature, which is, in turn, below the lingual tactile representation. The physical separation of the lingual somatosensory and taste representations by the intervening representation of the larynx in primates argues for a separate taste cortex, as does the localization of taste responses in agranular cortex and tactile and temperature responses in granular cortex in the rat (Kosar *et al.*, 1986). Furthermore, the taste representation is primarily uncrossed, whereas somatosensory representations are primarily crossed. Anterior lingual taste fields are represented rostral to posterior lingual fields in taste cortex, as they are at all lower levels. Thus, all central taste areas, brain stem to forebrain, are grossly somatotopically organized. In addition, a loose chemotopic organization of projections from the anterior lingual taste field is seen in the cortex. In the rat taste cortex, neurons most responsive to sucrose are found dorsal to neurons most responsive to NaCl, HCl, and quinine, which are located progressively more ventrally (Yamamoto, 1984). Response properties of taste-responsive neurons in primary taste cortex are complex. Inhibition/excitation, off responses, and increased stimulus specificity are seen in significant numbers of the neurons.

Recordings from primate primary taste cortex suggest a considerable specificity in taste responsiveness (Scott *et al.*, 1986). Many neurons respond to one stimulus category, and some neurons are most responsive to a natural mixture. Sweet sucrose, black currant juice (the mixture), and salty NaCl were the most effective taste stimuli. However, the great majority of neurons within the designated area are not taste responsive; <5% respond to taste stimuli, 10% respond to mouth movements, and 1% anticipate taste stimuli (Scott *et al.*, 1991). This scarcity of taste-responsive neurons makes the designation of the area as "primary sensory cortex" problematic. Neurons in the area project forward to the orbitofrontal cortex and back to the thalamic taste area in primates. In rodents, projections back to thalamic and brain stem taste areas are seen. These centrifugal projections could mediate effects of learning seen in the brain stem of rodents. Neurons in the secondary taste cortex of primates are influenced by motivational state; a response to a specific taste falls to zero as it is presented over and over again (Rolls *et al.*, 1989). By establishing response properties, these studies are beginning to unravel higher functions of cortical taste-responsive neurons.

IX. TASTE-MEDIATED BEHAVIORS: REFLEXES, PREFERENCES, APPETITES, CONDITIONED FOOD AVERSIONS, AND DISORDERS

Primary taste neurons play a role in the organization of many reflexive motor patterns, including swallowing, mastication, salivation, and acceptance/rejection. For example, introduction of a taste solution into the oral cavity of a normal or decerebrate mammal (including anencephalic infants) calls forth a series of complex movements or fixed action patterns (Grill and Berridge, 1985). In themselves these movements would result in ensuring that the solution was either retained or extruded from the oral cavity. The neural elements required are complete within the brain stem; the forebrain need not be involved. These motor patterns are associated with behaviors that, in intact animals that eat and drink, result in the expression of preferences and aversions. Amphetamines, which decrease appetite, do not affect elicitation of positive or negative fixed action patterns to taste stimuli in rats. However, benzodiazepines, which increase appetite, enhance positive reactions to taste stimuli (Treit and Berridge, 1990). This suggests a direct effect

of benzodiazepines on brain stem taste mechanisms rather than an effect secondary to anxiety reduction. Amphetamines, which stimulate the central nervous system, can result in decreased bitter thresholds (Mata, 1963). An increased ability to concentrate on the threshold task may account for this effect rather than increased taste sensitivity.

To many mammalian species, sugar solutions are palatable but quinine solutions are aversive. Sugar preferences are initiated by the activation of sugar-sensitive peripheral taste neurons in primates (Pfaffmann *et al.*, 1976) and hamsters (Rehnberg *et al.*, 1990). Some species prefer NaCl solutions of moderate strength when replete for sodium but prefer much stronger solutions when deprived of sodium. This sign of sodium appetite is associated with a decrease in responsiveness of primary taste neurons specialized for detecting sodium salts, which may reduce the natural aversiveness of strong salt solutions (Contreras and Frank, 1979). If responses of sodium-specialist afferents are inhibited, the animals neither show sodium appetite (Bernstein and Hennessy, 1987) nor distinguish between the tastes of sodium salts and non-sodium salts (Hill *et al.*, 1990). Innate taste preferences are not profoundly affected by lesions in forebrain taste areas. Thus, taste plays a role in reflexive behaviors. Chemicals for which appetities or preferences are shown are possibly identified by specialist neurons in peripheral nerves.

The sense of taste in many species plays a crucial role in the learning of food aversions (Garcia *et al.*, 1985). In species that identify foods by taste, associating gastrointestinal distress with a taste can be achieved in one trial. In subsequent trials, foods with that taste are avoided. Such aversions are not easily established to stimuli of other sensory modalities, including smell. However, a highly potent stimulus configuration for establishing food aversions is a taste-smell mixture. Taste-smell interactions, which frequently occur during eating, potentiate this special kind of learning. It occurs in humans (Logue, 1985) and is associated with chemotherapy (Bernstein, 1985), which may serve as the unconditioned stimulus. Food aversions cannot be learned by decerebrate animals. Specific food aversions are difficult to establish after lesions of the taste cortex, and aversions learned before lesioning the taste cortex are not recalled (Kiefer, 1985). Thus, the learning and retention of specific taste aversions requires the primary taste cortex.

People suffering from a taste loss (Frank and Smith, 1991) may fail to taste chemicals of particular taste qualities (specific ageusias) or may be less sensitive to all taste stimuli (hypogeusia) (Tomita *et al.*, 1986a and b; Bartoshuk, 1989). Failure to appreciate bitter substances in the normal range of concentrations occurs in the elderly and sometimes follows severe head trauma (Mott, 1992). The basis for bitter taste loss is unknown. Humans show a great range in ability to detect certain bitter substances (phenylthiocarbamide and related compounds; Figure 1). About one third of humans hardly detect the bitterness at all, a third find the compounds mildly bitter, but a third find the compounds extremely bitter (Lawless, 1987). The ability to detect the bitterness of phenylthiocarbamide appears to have a genetic basis. After some severe viral infections of the upper respiratory tract, a general hypogeusia appears that may persist for many years (Mott, 1991). The possibility that some viruses invade taste receptors or primary neurons, which are repaired in time, has been entertained.

Taste losses have also been associated with various drugs (Table 1). For example, medication with penicillamine (Keiser *et al.*, 1968) and captopril (Abu-Hamdan *et al.*, 1988), sulfhydryl-containing amino-acid derivatives, results in increased thresholds for the detection and recognition of sweet, salty, sour, and bitter compounds in some patients. Effects are greater after longer medication periods (>6 months) and higher doses (Abu-Hamdan *et al.*, 1988). Metallic dysgeusia is also reported as a side effect (see below). Low plasma and high urinary zinc levels have been measured in humans using these medications in some studies (Abu-Hamdan *et al.*, 1988), and severe zinc deficiency clearly produces taste deficits in animals (Catalanotto *et al.*, 1986). The ability of these drugs to chelate metal cations, particularly zinc, may be the immediate cause of taste losses.

The most disturbing taste disorder is dysgeusia, in which the sufferer chronically experiences an unpleasant taste (Scott, 1989). The

taste may be described as salty, bitter, or metallic, and is always unpleasant. The basis for this disorder is not known, although many medications are reported to produce dysgeusias (Mott, 1992). Difficulties with these reports, however, include (1) failure to exclude olfactory involvement (Gent *et al.*, 1987), (2) confusion of chemosensory terms, (3) small numbers of studied cases, and (4) unavoidable subjectivity (Mott, 1992).

Among other medications, those used in the treatment of bacterial infections, psychosis, arthritis, and hypertension can sometimes result in metallic dysgeusia (Table 2), the most common form of reported dysgeusia. The evidence for metallic tastes due to medications varies from reports of single rare cases (Magnasco and Magnasco, 1985) to surveys of large numbers of patients via questionnaires (Coulter, 1988). These reports indicate clearly that some medications, such as D-penicillamine (Hochberg, 1986), result in metallic dysgeusias in more than 25% of patients. Also, higher doses of medications such as Li_2CO_3 result in a greater incidence of metallic dysgeusia (Greenberg *et al.*, 1989). Most reports indicate disappearance of the dysgeusia quickly upon termination of the medication, but dysgeusias developed with some medications, such as captopril, can persist for months in some patients (Coulter, 1988).

Proposed mechanisms for metallic dysgeusia include the possibility that the medication, or biochemicals that are produced in response to the medication, appear in saliva or the blood supply of taste buds (Hellekant *et al.*, 1986) and directly activate the taste system. These chemicals could also activate the olfactory system, retronasally. Iron salts have no taste if the nose is clamped (Hettinger *et al.*, 1990) but have a metallic "taste" with the nose open. Patients who have had the chorda tympani sectioned in the middle ear may complain about a metallic taste (Grant *et al.*, 1989), and "metallic" is used frequently to describe the electric-taste sensation (Frank and Smith, 1991). Although eliminating direct contact of metal electrodes to the tongue results in a pure "sour" electric taste sensation (Bujas *et al.*, 1984), there is no reason to believe that the olfactory system would be activated after chorda tympani section. The term *metallic* may be used in reference to sensations mediated by the taste system or olfactory system, as is the term *sweet*.

X. SUMMARY

The sense of taste is an oral chemical sense that can influence health through diet. Taste receptor cells occur in taste buds that are distributed in oropharyngeal taste fields located on the anterior tongue, posterior tongue, palate, and epiglottis. Initial transduction of taste stimuli is thought to involve several mechanisms that utilize the properties of specific chemical stimuli. Transduction of ionic stimuli, which are primarily salty and sour, can utilize ion channels directly. Topical oral application of medications that affect ion channels profoundly affects ionic tastes. Nonionic stimuli, which are primarily sweet and bitter, likely bind proteinaceous receptors or otherwise affect cell membranes of receptor cells. Although aging progressively affects all taste qualities, lipophilic bitter taste is reduced most

TABLE 2
Some Medications Associated with Metallic Dysgeusia

Type	Name	Incidence (dose)[a]	Ref.
Antibiotic	Tetracycline	1 case (500 mg)	Magnasco
Antipsychotic	Li_2CO_3	7 of 47 (0.8 m*M*)	Greenberg
		0 of 47 (0.5 m*M*)	
Antiarthritic	Penicillamine	12 of 44 (125 mg)	Hochberg
Antihypertensive	Captopril	27 of 292	Coulter

[a] Serum levels are given for Li_2CO_3; amounts were prescribed: four per day (tetracycline), three per day (penicillamine); dose information for captopril was not provided.

and hydrophilic sweet taste least. Taste loss with aging is characterized by increased thresholds, but especially a decrease in perceived differences in stimulus intensity. Primary taste afferent neurons, which detect the different stimulus categories, are specialists or generalists and project via three cranial nerves to the nucleus of the solitary tract in the brain stem. Specialists primarily detect stimuli of one taste quality; generalists detect stimuli of several taste qualities. In primates, the gustatory rostral pole of the solitary nucleus projects to the ventral posteromedial thalamus, which in turn projects to the frontal opercular/insular cortex.

The different taste fields are represented topographically in brain stem and forebrain taste areas. Brain stem taste neurons receive complex patterns of input from primary afferent neurons. An individual brain stem neuron may respond to a single stimulus category in a single taste field. However, another neuron may respond to several stimulus categories in several taste fields. Forebrain taste neurons are, in general, more highly tuned to single stimulus categories than are brain stem neurons, although they are intermingled among many neurons that have no specific taste function. Primary taste afferent neurons and brain stem taste neurons play roles in ingestive reflexes and in the detection of nutrient sources for which innate preferences and appetites are shown.

Medications that affect the taste central nervous system may affect appetite. Learned food aversions, in which taste stimulation plays a crucial role, require taste forebrain areas for retention and specificity. A complete loss of taste is rare; perhaps because there are many taste fields. Taste losses can result from systemic medications that affect cell turnover or chelate metals. Some people are profoundly affected by taste disorders, particularly dysgeusia, which can result from systemic medications. Taste disorders cannot be reversed at present, but as more is learned about the sense of taste, treatments are likely to become available.

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REFERENCES

Abu-Hamdan, D. K., H. Desai, J. Sondheimer, J. Felicetta, S. Mahajans, and F. McDonald: Taste Acuity and Zinc Metabolism in Captopril-Treated Hypertensive Male Patients. *Am. J. Hypertens.* **1**:303S–308S (1988).

Akabas, M. H., J. Dodd, and Al-Awquati: A Bitter Substance Induces a Rise in Intracellular Calcium in a Subpopulation of Rat Taste Cells. *Science* **242**:107–1050 (1988).

Arvidson, K.: Location and Variation in Number of Taste Buds in Human Fungiform Papillae. *Scand. J. Dent. Res.* **87**:435–442 (1979).

Atema, J.: Structures and Functions in the Sense of Taste in the Catfish *(Ictalurus natalis). Brain Behav. Evol.* **4**:273–294 (1971).

Avenet, P. and S. C. Kinnamon: Cellular Basis of Taste Reception. *Curr. Opin. Neurobiol.* **1**:198–203 (1991).

Barry, M. A. and M. E. Frank: Response of the Gustatory System to Peripheral Nerve Injury. *Exp. Neurol.* **115**:60–64 (1992).

Bartoshuk, L. M.: Clinical Evaluation of the Sense of Taste. *Ear Nose Throat J.* **6**:331–337 (1989a).

Bartoshuk, L. M.: Taste: Robust Across the Age Span? *Nutrition and the Chemical Senses in Aging. Ann. N.Y. Acad. Sci.* **561**:65–75 (1989b).

Bartoshuk, L. M. and J. F. Gent: Taste Mixtures: an Analysis of Synthesis. **In:** *Taste, Olfaction, and the Central Nervous System,* pp. 210–232. (D. W. Pfaff, Ed.) The Rockefeller University Press, New York (1985).

Bartoshuk, L. M., B. Rifkin, L. E. Marks, and P. Bars: Taste and Aging. *J. Gerontol.* **41**:51–57 (1986).

Beckstead, R. M., J. R. Morse, and R. Norgren: The Nucleus of the Solitary Tract in the Monkey: Projections to the Thalamus and Brain Stem Nuclei. *J. Comp. Neurol.* **190**:259–282 (1980).

Beckstead, R. M. and R. Norgren: An Autoradiographic Examination of the Central Distribution of the Trigeminal, Facial, Glossopharyngeal, and Vagal Nerves in the Monkey. *J. Comp. Neurol.* **184**:455–472 (1979).

Beidler, L. M.: Innervation of Rat Fungiform Papilla. **In:** *Olfaction and Taste III,* pp. 352–369. (C. Pfaffmann, Ed.) The Rockefeller University Press, New York (1969).

Beidler, L. M. and R. L. Smallman: Renewal of Cells Within Taste Buds. *J. Cell. Biol.* **27**:263–272 (1965).

Bernstein, I. L.: Learned Food Aversions in the Progression of Cancer and Its Treatment, *Experimental Assessments and Clinical Applications of Conditioned Food Aversions. Ann. N.Y. Acad. Sci.* **443**:365–380 (1985).

Bernstein, I. L. and C. J. Hennessy: Amiloride-Sensitive Sodium Channels and Expression of Sodium Appetite in Rats. *Am. J. Physiol.* **253**:R371–374 (1987).

Boudreau, J. C., L. Sivakumar, L. T. Do, T. D. White, J. Oravec, and N. K. Hoang: Neurophysiology of Geniculate Ganglion (Facial Nerve) Taste Systems: Species Comparisons. *Chem. Senses* **10**:89–127 (1985).

Bradley, R. M., H. M. Stedman, and C. M. Mistretta: Superior Laryngeal Nerve Response Patterns to Chemical Stimulation of Sheep Epiglottis. *Brain Res.* **276**:81–93 (1983).

Bradley, R. M., H. M. Stedman, and C. M. Mistretta: Aging Does Not Affect Numbers of Taste Buds and Papillae in Adult Rhesus Monkeys. *Anat. Rec.* **212**:246–249 (1985).

Brosvic, G. M. and N. E. Hoey: Taste Detection and Discrimination Performance of Rats Following Selective Desalivation. *Physiol. Behav.* **48**:617–623 (1990).

Bujas, Z., D. Ajdukovic, and D. Mayer: Psychophysical Investigation of Taste Effects Provoked by Simultaneous Application of Taste Solutions and Electric Current. *Acta Biologica (Zagreb)* **10**:1–21 (1984).

Caprio, J.: Olfaction and Taste in the Channel Catfish: an Electrophysiological Study of the Responses to Amino Acids and Derivatives. *J. Comp. Physiol. A* **123**:357–371 (1978).

Caprio, J.: Peripheral Filters and Chemoreceptor Cells in Fishes. **In:** *Sensory Biology of Aquatic Animals,* pp. 313–338. (J. Atema, R. R. Fay, A. N. Popper, and W. N. Talvoga, Eds.) Springer-Verlag, New York (1988).

Catalanotto, F. A., M. E. Frank, and R. J. Contreras: Animal Models of Taste Alteration. **In:** *Clinical Measurement of Taste and Smell,* pp.429–442. (H. L. Meiselman and R. S. Rivlin, Eds.) Macmillan, New York (1986).

Cechetto, D. F.: Central Representation of Visceral Function. *Fed. Proc.* **46**:17–23 (1987).

Chang, F.-C.T. and T. R. Scott: Conditioned Taste Aversions Modify Neural Responses in the Rat Nucleus Tractus Solitarius. *J. Neurosci.* **4**:1850–1862 (1984).

Contreras, R. J., R. M. Beckstead, and R. Norgren: The Central Projections of the Trigeminal, Facial, Glossopharyngeal and Vagus Nerves: an Autoradiographic Study in the Rat. *J. Auton. Nerv. Syst.* **6**:303–322 (1982).

Contreras, R. J. and M. E. Frank: Sodium Deprivation Alters Neural Responses to Gustatory Stimuli. *J. Gen. Physiol.* **73**:567–594 (1979).

Coulter, D. M.: Eye Pain with Nifedipine and Disturbance of Taste with Captopril: a Mutually Controlled Study Showing a Method of Postmarketing Surveillance. *Br. Med. J.* **296**:1086–1088 (1988).

Cowart, B. J.: Relationships Between Taste and Smell Across the Adult Life Span. *Nutrition and the Chemical Senses in Aging. Ann. N.Y. Acad. Sci.* **561**:31–55 (1989).

Delay, R. J., J. C. Kinnamon, and S. D. Roper: Ultrastructure of Mouse Vallate Taste Buds. II. Cell Types and Cell Lineage. *J. Comp. Neurol.* **253**:242–252 (1986).

DeSimone, J. A., G. L. Heck, S. Mierson, and S. K. Desimone: The Active Ion Transport Properties of Canine Lingual Epithelia in Vitro. *J. Gen. Physiol.* **83**:633–656 (1984).

Dodd, J. and V. F. Castellucci: Smell and Taste: the Chemical Senses. **In:** *Principles of Neural Science* (3rd ed.), pp. 512–529. (E. R. Kandel, J. H. Schwartz, and T. M. Jessell, Eds.) Elsevier, New York (1991).

Elliot, E. J. and S. A. Simon: The Anion in Salt Taste: a Possible Role for Paracellular Pathways. *Brain Res.* **535**:9–17 (1990).

Erickson, R. P.: Definitions: a Matter of Taste. **In:** *Taste, Olfaction, and the Central Nervous System,* pp. 129–150. (D. W. Pfaff, Ed.) The Rockefeller University Press, New York (1985).

Farbman, A. I.: Renewal of Taste Buds in Rat Circumvallate Papilla. *Cell. Tissue Kinetics* **13**:349–357 (1980).

Finger, T. E.: Gustatory Nuclei and Pathways in the Central Nervous System. **In:** *Neurobiology of Taste and Smell,* pp. 331–353. (T. E. Finger and W. L. Silver, Eds.) John Wiley & Sons, New York (1987).

Formaker, B. K. and D. L. Hill: Lack of Amiloride Sensitivity in SHR and WKY Glossopharyngeal Taste Responses to NaCl. *Physiol. Behav.* **50**:765–769 (1991).

Frank, M. E.: Taste-Responsive Neurons of the Glossopharyngeal Nerve of the Rat. *J. Neurophysiol.* **65**:1452–1463 (1991).

Frank, M. E., S. L. Bieber, and D. V. Smith: The Organization of Taste Sensibilities in Hamster Chorda Tympani Nerve Fibers. *J. Gen. Physiol.* **91**:861–896 (1988).

Frank, M. E., R. J. Contreras, and T. P. Hettinger: Nerve Fibers Sensitive to Ionic Taste Stimuli in the Chorda Tympani of the Rat. *J. Neurophysiol.* **50**:941–960 (1983).

Frank, M. E. and G. H. Nowlis: Learned Aversions and Taste Qualities in Hamsters. *Chem. Senses* **14**:379–394 (1989).

Frank, M. E. and D. V. Smith: Electrogustometry: a Simple Way to Test Taste. **In:** *Smell and Taste in Health and Disease,* pp. 503–514. (T. V. Getchell, R. L. Doty, L. M. Bartoshuk, and J. B. Snow, Eds.) Raven Press, New York (1991).

Garcia, J., P. A. Lasiter, F. Bermudez-Rattoni, and D. A. Deems: A General Theory of Aversion Learning, *Experimental Assessments and Clinical Applications of Conditioned Food Aversions. Ann. N.Y. Acad.Sci.* **443**:8–21 (1985).

Gardner, J. F. and K. G. Gray: Chlorhexidine. **In:** *Disinfection, Sterilization, and Preservation,* pp. 251–270. (S. S. Block, Ed.) Lea and Febiger, Philadelphia (1983).

Gent, J. F., R. B. Goodspeed, R. T. Zagraniski, and F. A. Catalanotto: Taste and Smell Problems: Validation of Questions for the Clinical History. *Yale J. Biol. Med.* **60**:27–35 (1987).

Gilmore, M. M. and C. Murphy: Aging Is Associated with Increased Weber Ratios for Caffeine, but Not for Sucrose. *Percept. Psychophys.* **46**:555–559 (1989).

Giza, B. K. and Scott: The Effect of Amiloride on Taste-Evoked Activity in the Nucleus Tractus Solitarius of the Rat. *Brain Res.* **550**:247–256 (1991).

Grant, R., S. Miller, D. Simpson, P. J. Lamey, and I. Bones: The Effect of Chorda Tympani Section on Ipsilateral and Contralateral Salivary Secretion and Taste in Man. *J. Neurol. Neurosurg. Psychiat.* **52**:1058–1062 (1989).

Greenberg, A. J., J. M. Kane, M. B. Keller, P. Lavori, J. F. Rosenbaum, K. Cole, and J. Lavelle: Comparison of Standard and Low Serum Levels of Lithium for Maintenance Treatment of Bipolar Disorder. *N. Engl. J. Med.* **321**:1489–1493 (1989).

Grill, H. J. and K. C. Berridge: Taste Reactivity as a Measure of the Neural Control of Palatability. *Prog. Psychobiol. Physiol. Psychol.* **11**:1–61 (1985).

Grzegorczyk, P. B., S. W. Jones, and C. M. Mistretta: Age-Related Differences in Salt Taste Acuity. *J. Gerontol.* **34**:834–840 (1979).

Hall, M. J., L. M. Bartoshuk, W. C. Cain, and J. C. Stevens: PTC Taste Blindness and the Taste of Caffeine. *Nature* **253**:442–443 (1975).

Halsell, C. B.: Organization of Parabrachial Nucleus Efferents to the Thalamus and Amygdala in the Golden Hamster. *J. Comp. Neurol.* **317**:57–78 (1992).

Halsell, C. B. and M. E. Frank: Mapping Study of the Parabrachial Taste-Responsive Area for the Anterior Tongue in the Golden Hamster. *J. Comp. Neurol.* **306**:708–722 (1991).

Hamilton, R. B. and R. Norgren: Central Projections of Gustatory Nerves in the Rat. *J. Comp. Neurol.* **222**:560–577 (1984).

Hanamori, T., I. J. Miller, and D. V. Smith: Gustatory Responsiveness of Fibers in the Hamster Glossopharyngeal Nerve. *J. Neurophysiol.* **60**:478–498 (1988).

Harper, H. W.: A Diffusion Potential Model of Salt Taste Receptors. *Olfaction and Taste IX, Ann. N.Y. Acad. Sci.* **510**:349–351 (1987).

Hayama, T. and J. Caprio: Lobule Structure and Somatotopic Organization of the Medullary Facial Lobe in the Channel Catfish Ictalurus Punctatus. *J. Comp. Neurol.* **285**:9–17 (1989).

Hellekant, G., D. Glaser, J. Brouwer, and H. Van der Wel: Gustatory Responses in Three Prosimian and Two Simian Primate Species to Six Sweeteners and Miraculin and Their Phylogenetic Implications. *Chem. Senses* **6**:165–173 (1981).

Hellekant, G., H. Van der Wel, J. N. Brouwer, C. Hard af Segerstad, and T. W. Roberts: Chorda Tympani Proper Nerve Responses to Intra-Arterial and Surface Stimulation of the Tongue in Rhesus Monkey and Rat. *Chem. Senses* **11**:557–566 (1986).

Helms, J. and M. Frank: Chlorhexidine Glucontate's Effects on Taste Perception and Taste Nerve Responses. *J. Dent. Res.* **68**:951 (1989).

Herness, M. S.: The Receptor Potential to Iontophoretic Stimuli and Its Relevance to Electrogustometry. **In:** *The Beidler Symposium on Taste and Smell,* pp. 83–92. (I. J. Miller, Jr., Ed.) Book Service Associates, Winston-Salem, NC (1988).

Hettinger, T. P. and M. E. Frank: Specificity of Amiloride Inhibition of Hamster Taste Responses. *Brain Res.* **513**:24–34 (1990).

Hettinger, T. P., W. E. Myers, and M. E. Frank: Role of Olfaction in Perception of Non-Traditional "Taste" Stimuli. *Chem. Senses* **15**:755–760 (1990).

Hill, D. L.: Development and Plasticity of the Gustatory System. **In:** *Neurobiology of Taste and Smell,* pp. 379–400. (T. E. Finger and W. L. Silver, Eds.) John Wiley & Sons, New York (1987).

Hill, D. L., B. K. Formaker, and K. S. White: Perceptual Characteristics of the Amiloride-Suppressed Sodium Chloride Taste Response in the Rat. *Behav. Neurosci.* **104**:734–741 (1990).

Hochberg, M. C.: Auranofin or D-Penicillamine in Treatment of Rheumatoid Arthritis. *Ann. Int. Med.* **105**:528–535 (1986).

Hou-Jensen, H. M.: Die Papillae Foliatae des Menschen. *Z. Anat. Enwicklungsgeschichte* **102**:348–388 (1933).

Jacobs, K. M., G. P. Mark, and T. R. Scott: Taste Responses in the Nucleus Tractus Solitarius of Sodium-Deprived Rats. *J. Physiol.* **406**:393–410 (1988).

Jakinovich, W. and D. Sugarman: Sugar Taste Reception in Mammals. *Chem. Senses* **13**:13–32 (1988).

Keiser, H. R., R. I, Henkin, F. C. Bartter, and A. Sjoerdsma: Loss of Taste During Therapy with Penicillamine. *JAMA* **203**:381–383 (1968).

Kiefer, S. W.: Neural Mediation of Conditioned Food Aversions. *Experimental Assessments and Clinical Applications of Conditioned Food Aversions, Ann. N.Y. Acad. Sci.* **443**:100–109 (1985).

Kinnamon, J. C.: Organization and Innervation of Taste Buds. **In:** *Neurobiology of Taste and Smell,* pp. 277–297. (T. E. Finger and W. L. Silver, Eds.) John Wiley & Sons, New York (1987).

Kinnamon, S. C.: Taste Transduction: a Diversity of Mechanisms. *Trends Neurosci.* **11**:491–496 (1988).

Kinnamon, S. C., V. E. Dionne, and K. G. Beam: Apical Localization of K^+ Channels in Taste Cells Provides the Basis for Sour Taste Transduction. *Proc. Natl. Acad. Sci. U.S.A.* **85**:7023–7027 (1988).

Kinnamon, S. C. and S. D. Roper: Passive and Active Membrane Properties of Mudpuppy Taste Receptor Cells. *J. Gen. Physiol.* **91**:351–372 (1987).

Kinnamon, S. C. and S. D. Roper: Membrane Properties of Isolated Mudpuppy Taste Cells. *J. Gen. Physiol.* **91**:351–372 (1988).

Kosar, E., H. J. Grill, and R. Norgren: Gustatory Cortex in the Rat. I. Physiological Properties and Cytoarchitecture. *Brain Res.* **379**:329–341 (1986).

Krarup, B.: Electro-Gustometry: a Method for Clinical Taste Examinations. *Acta Otolaryngol. (Stockholm)* **49**:294–305 (1958).

Lang, N. P., F. A. Catalanotto, R. U. Knopfli, and A. A. A. Antczak: Quality-Specific Taste Impairment Following the Application of Chlorhexidine Digluconate Mouth Rinses. *J. Clin. Periodontol.* **15**:43–48 (1988).

Lawless, H. T.: Gustatory Psychophysics. **In:** *Neurobiology of Taste and Smell,* pp. 401–420. (T. E. Finger and W. L. Silver, Eds.) John Wiley & Sons, New York (1987).

Logue, A. W.: Conditioned Food Aversion Learning in Humans, *Experimental Assessments and Clinical Applications of Conditioned Food Aversions. Ann. N.Y. Acad. Sci.* **443**:316–329 (1985).

Magnasco, L. D. and A. J. Magnasco: Metallic Taste Associated with Tetracycline Therapy. *Clin. Pharm.* **4**:455–456 (1985).

Mata, F.: Effect of Dextro-Amphetamine on Bitter Taste Threshold. *J. Neuropsychiat.* **4**:315–320 (1963).

Mattes, R. D., C. M. Christensen, and K. Engelman: Effects of Therapeutic Doses of Amiloride and Hydroch-

lorothiazide on Taste, Saliva and Salt Intake in Normotensive Adults. *Chem. Senses* **13**:33–44 (1988).

McBride, M. R. and C. M. Mistretta: Taste Responses from the Chorda Tympani Nerve in Young and Old Fischer Rats. *J. Gerontol.* **41**:306–314 (1986).

Miller, I. J., Jr.: Human Taste Bud Density Across Adult Age Groups. *J. Gerontol.* **43**:26–30 (1988).

Miller, I. J., Jr.: Variation in Human Taste Bud Density as a Function of Age. *Nutrition and the Chemical Senses in Aging, Ann. N.Y. Acad. Sci.* **561**:307–319 (1989).

Miller, I. J., Jr. and L. M. Bartoshuk: Taste Perception, Taste Bud Distribution, and Spatial Relationships. **In:** *Smell and Taste in Health and Disease,* pp. 205–233. (T. V. Getchell, R. L. Doty, L. M. Bartoshuk, and J. B. Snow, Eds.) Raven Press, New York (1991).

Mistretta, C. M.: Anatomy and Neurophysiology of the Taste System in Aged Animals, *Nutrition and the Chemical Senses in Aging. Ann. N.Y. Acad. Sci.* **561**:277–290 (1989).

Mistretta, C. M. and I. A. Oakley: Quantitative Anatomical Study of Taste Buds in Fungiform Papillae of Young and Old Fischer Rats. *J. Gerontol.* **41**:315–318 (1986).

Moncrieff, R. W.: *The Chemical Senses.* Leonard Hill, London (1967).

Moore, L. M., C. R. Nielson, and C. M. Mistretta: Sucrose Taste Thresholds: Age-Related Differences. *J. Gerontol.* **37**:64–69 (1982).

Mott, A. E.: Olfactory and Gustatory Dysfunction: General Medical Examination. *J. Head Trauma Rehab.* In press (1992).

Mott, A. E. and D. A. Leopold: Disorders in Taste and Smell. *Med. Clin. N. Am.* **75**:1–33 (1991).

Murphy, C. and M. M. Gilmore: Quality-Specific Effects of Aging on the Human Taste System. *Percept. Psychophys.* **45**:121–128 (1989).

Murphy, C. and J. Withee: Age-Related Differences in the Pleasantness of Chemosensory Stimuli. *Psychol. Aging* **1**:312–318 (1986).

Nagai, T., C. M. Mistretta, and R. M. Bradley: Developmental Decrease in Size of Peripheral Receptive Fields of Single Chorda Tympani Nerve Fibers and Relation to Increasing NaCl Taste Sensitivity. *J. Neurosci.* **8**:64–72 (1988).

Nejad, M. S.: The Neural Activities of the Greater Superficial Petrosal Nerve of the Rat in Response to Chemical Stimulation of the Palate. *Chem. Senses* **11**:283–293 (1986).

Ninomiya, Y. and M. Funakoshi: Amiloride Inhibition of Responses of Rat Single Chorda Tympani Responses to Chemical and Electrical Tongue Stimulations. *Brain Res.* **451**:319–325 (1988).

Ninomiya, Y. and M. Funakoshi: Selective Procaine Inhibition of Rat Chorda Tympani Responses to Electric Taste Stimulation. *Comp. Biochem. Physiol.* **92A**:185–188 (1989).

Ninomiya, Y., T. Mizukoshi, T. Nishikawa, and M. Funakoshi: Ion Specificity of Rat Chorda Tympani Fibers to Chemical and Electrical Tongue Stimulations. *Brain Res.* **404**:350–354 (1987).

Nishijo, H. and R. Norgren: Responses from Parabrachial Gustatory Neurons in Behaving Rats. *J. Neurophysiol.* **63**:707–724 (1990).

Norgren, R.: Central Neural Mechanisms of Taste. **In:** *Handbook of Physiology. The Nervous System. Sensory Processes,* Vol. 3, Pt. 2, pp. 1087–1128. I. (Darian-Smith, Vol. Ed., J. M. Brookhart and V. B. Mountcastle, Sect. Eds.) Am. Physiol. Soc., Bethesda (1984).

Norgren, R. and C. M. Leonard: Ascending Central Gustatory Pathways. *J. Comp. Neurol.* **150**:217–238 (1971).

Nowlis, G. H., M. E. Frank, and C. Pfaffmann: Specificity of Acquired Aversions to Taste Qualities in Hamsters and Rats. *J. Comp. Physiol. Psychol.* **94**:932–942 (1980).

Oakley, B.: Receptive Fields of Cat Taste Fibers. *Chem. Senses* **1**:431–442 (1975).

Oakley, B.: Trophic Competence in Mammalian Gustation. **In:** *Taste, Olfaction, and the Central Nervous System,* pp. 289–298. (D. W. Pfaff, Ed.) The Rockefeller University Press, New York (1985).

Ogawa, H., T. Imoto, and T. Hayama: Responsiveness of Solitario-Parabrachial Relay Neurons to Taste and Mechanical Stimulation Applied to Oral Cavity in Rats. *Exp. Brain. Res.* **54**:349–358 (1984).

Pfaffmann, C.: Physiological and Behavioral Processes of the Sense of Taste. **In:** *Ciba Foundation Symposium on Taste and Smell in Vertebrates,* pp. 31–50. (G. E. W. Wolstenholme and J. Knight, Eds.) J. A. Churchill, London (1970).

Pfaffmann, C., M. Frank, L. M. Bartoshuk, and T. C. Snell: Coding Gustatory Information in the Squirrel Monkey Chorda Tympani. *Prog. Psychobiol. Physiol. Psychol.* **6**:1–27 (1976).

Pritchard, T. C., R. B. Hamilton, J. R. Morse, and R. Norgren: Projections of Thalamic Gustatory and Lingual Areas in the Monkey. *J. Comp. Neurol.* **244**:213–228 (1986).

Pritchard, T. C., R. B. Hamilton, and R. Norgren: Neural Coding of Gustatory Information in the Thalamus of Macaca mulatta. *J. Neurophysiol.* **61**:1–14 (1989).

Rehnberg, B. G., T. P. Hettinger, and M. E. Frank: The Role of Sucrose-Sensitive Neurons in Ingestion of Sweet Stimuli by Hamsters. *Physiol. Behav.,* **48**:459–466 (1990).

Rollin, H.: Drug-Related Gustatory Disorders. *Ann. Otol.* **87**:37–42 (1978).

Rolls, E. T., Z. J. Sienkiewicz, and S. Yaxley: Hunger Modulates the Responses to Gustatory Stimuli of Single Neurons in the Caudolateral Orbitofrontal Cortex of the Macaque Monkey. *Eur. J. Neurosci.,* **1**:53–60 (1989).

Roper, S. D.: The Cell Biology of Vertebrate Taste Receptors. *Ann. Rev. Neurosci.* **12**:329–353 (1989).

Sato, K. and R. Kamata: Quantitative Examination of Taste Deficiency Due to Radiation Therapy. *Radiat. Med.* **2**:61–70 (1984).

Sato, T. and L. M. Beidler: Membrane Resistance Change in the Frog Taste Cells in Response to Water and NaCl. *J. Gen. Physiol.* **66**:735–763 (1975).

Schiffman, S. S.: Taste and Smell in Disease. *N. Engl. J. Med.* **308**:1275–1279, 1337–1343 (1983).

Schiffman, S. S., A. L. Crumbliss, Z. S. Warwick, and B. G. Graham: Thresholds for Sodium Salts in Young and Elderly Human Subjects: Correlation with Molar Conductivity of Ion. *Chem. Senses* **15**:671–678 (1990).

Schiffman, S. S., M. G. Lindley, T. B. Clark, and C. Makino: Molecular Mechanism of Sweet Taste: Relationship of Hydrogen Bonding to Taste Sensitivity for Both Young and Elderly. *Neurobiol. Aging* **2**:173–185 (1981).

Schiffman, S. S., E. Lockhead, and F. W. Maes: Amiloride Reduces the Taste Intensity of Na^+ and Li^+ Salts and Sweeteners. *Proc. Natl. Acad. Sci. U.S.A.* **80**:6136–6140 (1983).

Schiffman, S. S., S. A. Simon, J. M. Gill, and T. G. Beeker: Bretylium Tosylate Enhances Salt Taste. *Physiol. Behav.* **36**:1129–1137 (1986).

Schiffman, S. S. and Z. S. Warwick: Use of Flavor-Amplified Foods to Improve Nutritional Status in Elderly Persons, *Nutrition and the Chemical Senses in Aging. Ann. N.Y. Acad. Sci.* **561**:267–276 (1989).

Schiller, J. H., J. Rozental, K. D. Tutsch, and D. L. Trump: Inadvertent Administration of 480 mg/m² of Cisplatin. *Am. J. Med.* **86**:624–625 (1989).

Schulkin, J.: *Sodium Hunger: The Search for a Salty Taste.* Cambridge University Press, New York (1991).

Scott, A. E.: Characteristics of Taste and Smell Disorders. *Ear Nose Throat J.* **68**:297–315 (1989).

Scott, T. R. and B. K. Giza: Coding Channels in the Taste System of the Rat. *Science* **249**:1585–1587 (1990).

Scott, T. R., C. R. Plata-Salaman, V. L. Smith, and B. K. Giza: Gustatory Neural Coding in the Monkey Cortex: Stimulus Intensity. *J. Neurophysiol.* **65**:76–86 (1991).

Scott, T. R., S. Yaxley, Z. J. Sienkiewicz, and E. T. Rolls: Gustatory Responses in the Frontal Opercular Cortex of the Alert Cynomolgus Monkey. *J. Neurophysiol.* **56**:876–890 (1986a).

Scott, T. R., S. Yaxley, Z. J. Sienkiewicz, and E. T. Rolls: Gustatory Responses in the Nucleus Tractus Solitarius of the Alert Cynomolgus Monkey. *J. Neurophysiol.* **55**:182–200 (1986b).

Smith, D. V. and T. Hanamori: Organization of Gustatory Sensitivities in Hamster Superior Laryngeal Nerve Fibers. *J. Neurophysiol.* **65**:1098–1114 (1991).

Smith, D. V., R. L. Van Buskirk, J. B. Travers, and S. L. Bieber: Coding of Taste Stimuli by Hamster Brain Stem Neurons. *J. Neurophysiol.* **50**:541–558 (1983).

Soni, N. K. and P. Chatterji: Gustotoxicity of Bleomycin. *Otorhinolaryngology* **47**:101–105 (1985).

Teeter, J. H. and J. G. Brand: Peripheral Mechanisms of Gustation: Physiology and Biochemistry. **In:** *Neurobiology of Taste and Smell,* pp. 299–329. (T. E. Finger and W. L. Silver, Eds.) John Wiley & Sons, New York (1987).

Teeter, J. H. and G. H. Gold: A Taste of Things to Come. *Nature* **331**:298–299 (1988).

Tomita, H. and Y. Horikawa: Dissociated Taste Disorder. *Auris-Nasus-Larynx (Tokyo)* **13** (Suppl. I):S17–23 (1986).

Tomita, H., M. Ikeda, and Y. Okuda: Basis and Practice of Clinical Taste Examinations. *Auris-Nasus-Larynx (Tokyo)* **13** (Suppl. I):S1–15 (1986).

Travers, J. B.: Efferent Projections from the Anterior Nucleus of the Solitary Tract of the Hamster. *Brain Res.* **457**:1–11 (1988).

Travers, J. B., S. P. Travers, and R. Norgren: Gustatory Neural Processing in the Hindbrain. *Annu. Rev. Neurosci.* **10**:595–632 (1987).

Travers, S. P. and R. Norgren: Coding the Sweet Taste in the Nucleus of the Solitary Tract: Differential Roles for Anterior Tongue and Nasoincisor Duct Gustatory Receptors. *J. Neurophysiol.* **65**:1372–1380 (1991).

Travers, S. P., C. Pfaffmann, and R. Norgren: Convergence of Lingual and Palatal Gustatory Neural Activity in the Nucleus of the Solitary Tract. *Brain Res.* **365**:305–320 (1986).

Travers, S. P. and D. V. Smith: Responsiveness of Neurons in the Hamster Parabrachial Nuclei to Taste Mixtures. *J. Gen. Physiol.* **84**:221–250 (1984).

Treit, D. and K. C. Berridge: A Comparison of Benzodiazepine, Serotonin, and Dopamine Agents in the Taste-Reactivity Paradigm. *Pharm. Biochem. Behav.* **37**:451–456 (1990).

Vogt, M. B. and C. M. Mistretta: Convergence in Mammalian Nucleus of Solitary Tract During Development and Functional Differentiation of Salt Taste Circuits. *J. Neurosci.* **10**:3148–3157 (1990).

Walters, D. E., F. T. Orthoefer, and G. E. DuBois: *Sweeteners: Discovery, Molecular Design, Chemoreception.* American Chemical Society, Washington, DC (1991).

Weiffenbach, J. M.: Taste Perception Mechanisms. *Front Oral Physiol.* **6**:151–167 (1987).

Weiffenbach, J. M., B. J. Baum, and R. Burghauser: Taste Thresholds: Quality Specific Variation with Human Aging. *J. Gerontol.* **37**:372–377 (1982).

Weiffenbach, J. M., B. J. Cowart, and B. J. Baum: Taste Intensity Perception in Aging. *J. Gerontol.* **41**:460–468 (1986).

Whitehead, M. C.: Neuronal Architecture of the Nucleus of the Solitary Tract in the Hamster. *J. Comp. Neurol.* **276**:547–572 (1986).

Whitehead, M. C., C. S. Beeman, and B. A. Kinsella: Distribution of Taste and General Sensory Nerve Endings in Fungiform Papillae of the Hamster. *Am. J. Anat.* **173**:185–201 (1985).

Whitehead, M. C. and M. E. Frank: Anatomy of the Gustatory System of the Hamster: Central Projections of the Chorda Tympani and the Lingual Nerve. *J. Comp. Neurol.* **220**:378–395 (1983).

Whitehead, M. C., M. E. Frank, T. P. Hettinger, L.-T. Hou, and H.-D. Nah: Persistence of Taste Buds in Denervated Fungiform Papillae. *Brain Res.* **405**:192–195 (1987).

Yamamoto, T.: Taste Responses of Cortical Neurons. *Prog. Neurobiol.* **23**:273–315 (1984).

Ye, Q., G. L. Heck, and J. A. DeSimone: The Anion Paradox in Sodium Taste Reception: Resolution by Voltage-Clamp Studies. *Science* **254**:724–726 (1991).